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Specific comments to authors

In this review manuscript, the authors aimed to review the types of non-apoptotic regulated cell deaths (RCDs), in particular pyroptosis, ferroptosis, and necroptosis in the occurrence of Nonalcoholic fatty liver disease (NAFLD) and its progression towards steatohepatitis and cancer, with potential impact in diagnostic and therapeutic approaches. The review is well-written and presented.

However, in my opinion, the potential clinical/therapeutic impact should be improved by discussing the potential improvement of available and under investigation systemic treatments for hepatocellular carcinoma (HCC). In particular, it has been previously demonstrated that Metronomic capecitabine promotes ferroptosis (Int Immunopharmacol. 2023 Nov;124(Pt A):110810. doi: 10.1016/j.intimp.2023.110810.) which can be an adjunctive antitumor therapeutic mechanism to further investigate in hepatocellular carcinoma.

Reply: The authors would like to appreciate your valuable and priceless comment which has undeniably improved the scientific content of the article. The studies suggesting the potential of metronomic capecitabine and other chemicals to promote ferroptosis is discussed in the revised version of the manuscript (highlighted in **yellow**).

In this regard, the authors should recall the recently published cohort studies demonstrating both anti-tumor efficacy and safety of metronomic capecitabine in HCC patients unresponsive to the tyrosine kinase inhibitor sorafenib or intolerant to first-line sorafenib, as previously demonstrated (Dig Liver Dis. 2015 Jun;47(6):518-22. doi: 10.1016/j.dld.2015.03.010; J Cancer Res Clin Oncol. 2018 Feb;144(2):403-414. doi: 10.1007/s00432-017-2556-6).

Reply: Thanks to your priceless comment that significantly improved the scientific content of the manuscript suggested sources have been discussed (highlighted in



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green).

Importantly, the authors should recall the recent development of combination treatment strategies for HCC patients based on the combination of tyrosine kinase inhibitors and/or anti-VGFR agents plus immune checkpoint inhibitors, as well-described in a recent comprehensive review (TKIs in combination with immunotherapy for hepatocellular carcinoma. *Expert Rev Anticancer Ther.* 2023 Mar;23(3):279-291. doi: 10.1080/14737140.2023.2181162.), to explore which combined treatment have more favorable effect on pyroptosis, ferroptosis, and necroptosis.

Reply: By appreciating your valuable suggestion, the studies evaluating the efficacy of TKIs in combination with immunotherapy in HCC is discussed (highlighted in **turquoise**).